REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office Action dated October 16, 2003 are respectfully requested. Applicants petition for a one-month extension of time in which to file this response. A separate petition is enclosed.

I. Amendments

A. Specification

The values in Table 1 on page 8 of the specification are amended to recite the correct drug/lipid ratios and to specify that the ratios are mol/mol ratios. Table 3 on page 11 is similarly amended to set forth the correct molar drug/lipid ratios. The corresponding description of Table 3 on page 11, at lines 16 and 19 is also amended to recite the correct drug/lipid ratios.

With regard to correction of an incorrectly disclosed characteristic that is inherent, the U.S. PTO Board of Patent Appeals and Interferences stated that the question was one of "changing the original description of a product which...was described by sufficient characteristics to distinguish it" and that "the products described, exemplified and claimed by Appellants inherently had and have now the structure given in the amendment in question." The board held "the changes made in this amendment do not constitute new matter." Ex Parte Marsili, 214 USPQ 904 (Board Pat. App. & Int. 1979).

Likewise, the Federal Circuit has found that no new matter was added in an amendment correcting a structural formula because there was sufficient evidence to show that the added structure was an inherent and more accurate description of the disclosed subject matter. Specifically, "[t]he amendments did not describe different inventions; they only clarified and corrected the erroneous characterization of the already disclosed inventions. Such amendments do not add or change the nature of the disclosed inventions." Regents of the University of New Mexico v. Knight, 321 F.3d 1111, 66 USPQ2d 1001 (Fed. Cir. 2003).

In the present application, calculation of drug-to-lipid ratios is easily done by those of skill in the art. The molar drug/lipid ratio for each composition described in Table 1 and Table 3 is simply the mole fraction of drug divided by the sum of the lipid

mole fractions. For example, the liposome composition specified on page 7 (line 26) and on page 10 (line 37) as 89/5/6 has a molar drug to lipid ratio of 6/94, or 0.06.

Applicants submit that the changes to the specification are not new matter. It is well-established in the case law that amendatory material is not new matter where it is concerned with an inherent characteristics of an illustrative product of an invention already sufficiently identified in the original patent disclosure. (In re Nathan, Hogg, and Schneider, 140 USPQ 601 (CCPA, 1964). The amendatory material provided here is directly related to an inherent characteristic of the composition described. Moreover, the amendatory material is readily derivable by a person skilled in the art of the claimed invention using the liposome formulations recited in the specification and, if needed, recognized sources (e.g., journal articles and trade information) to calculate the drug/lipid ratio. Thus, no new matter is introduced by these amendments to the specification.

B. Claims

Claims 1, 10, and 22 are amended to recite that the lipid-derivatized radiosensitizer is added in an amount sufficient to provide a drug-to-lipid molar ratio of between about 0.06-0.67. Basis is found in the liposome formulations specified in the description and in the data set forth in the specification in Tables 1 and 3, as discussed above.

II. Rejections under 35 U.S.C. § 103

Claims 1-30 were rejected under 35 U.S.C. §103 as being obvious over Martin *et al.*, U.S. Patent No. 5,213,804 in view of Mori *et al.* (*Cancer Chemother. Pharmacol.*, 35:447 (1995)).

Claims 1-30 were rejected under 35 U.S.C. §103 as being obvious over Martin *et al.* in view of Mori *et al.* further in view of Kassis, U.S. Patent No. 5,077,034.

These rejections are respectfully traversed for the following reasons.

A. The Present Invention

The present invention is concerned with the problem in the liposome art of providing and preparing a liposome composition that includes a lipid-derivatized drug in a high drug/lipid ratio. Liposome formulations with a high drug/lipid ratio, when the drug is a lipid-derivatized drug, are difficult to size via extrusion, as discussed on page 7, lines 5-19 of the specification. Thus, the present invention provides a liposome composition having a significantly higher drug/lipid ratio, where the drug is a lipid-derivatized radiosensitizer.

B. The Cited Art

MARTIN *ET AL.* describe liposomes having an entrapped anti-tumor compound and a surface coating of hydrophilic polymer chains.

MORI *ET AL.* describe liposomes having a lipid-derivatized radiosensitizer and antibodies attached to the liposome surface.

KASSIS *ET AL.* describe treatment of a tumor using a radiohalogenated pyrimidine compound, such as IudR.

C. Analysis: Rejection over Martin *et al.* in view of Mori *et al.*

The invention as set forth in the presently amended claims require that the drug/lipid (mol/mol) ratio be between 0.06-0.67. As discussed above, liposome compositions having a high drug/lipid ratio are desired from a therapeutic standpoint, but are difficult to provide, particularly when the drug is derivatized with a lipid. Liposome compositions that include a lipid-derivatized drug are known to be difficult to size via extrusion, thus limiting the amount of lipid-derivatized drug that can be added to the formulation and resulting in a low drug/lipid ratio. The liposome composition of the present invention provides a molar drug/lipid ratio of between 0.06-0.67.

In contrast, the composition described by Mori *et al.* has a molar drug/lipid ratio of 0.03. A detailed analysis of the drug/lipid ratios for the composition disclosed in Mori *et al.* compared to two of the compositions of the present invention is provided in Appendix A, attached herewith. As seen, the formulation described in Mori *et al.*

includes 3 mole percent dpFuDR, for a drug/lipid ratio of 0.03. The formulation of the present invention having 6 mole percent dplUdR has a drug/lipid ratio of 0.06. The formulation of the present invention having 15 mole percent dplUdR has a drug/lipid ratio of 0.17. Thus, the invention provides a composition that has two-times or more drug than in the composition described by Mori *et al.*

In another paper by Mori *et al.*, (*Pharmaceutical Research*, 10(4):507 (1993); "Mori *et al.*-2", copy submitted herewith by way of information disclosure statement Form 1449, liposomes prepared from egg phosphatidylcholine, cholesterol, lipid-derivatized PEG, and dpFUdR are described. The dpFUdR is added at 3 mole percent. Mori *et al.* state:

> "Incorporation of all three lipophilic prodrugs at 3.0 mol% of the lipid mixture did not cause aggregation or precipitation of drugs and/or liposomes before or after the extrusion procedure.....Incorporation of lipophilic prodrugs at higher concentrations inhibited the extrusion procedure due to insoluble unincorporated drug molecules." (Mori *et al.*-2, page 509, Col. 1, first paragraph under "Results" section).

Thus, in both of the Mori *et al.* documents, the liposome composition disclosed is limited to 3 mol% of lipid-derivatized drug, with a drug/lipid ratio of 0.03. It would not be obvious to increase the amount of drug in the liposome composition of Mori *et al.*, since there would be no expectation of success in preparing a composition having suitable sizes for in vivo use based on the teaching in Mori *et al.*-2, that compositions with more than 3 mol% of drug could not be sized.

Thus, the combination of Martin *et al.* and Mori *et al.* provides, at most, a teaching of a liposome composition where the drug/lipid ratio is 0.03 or less.

In contrast, the present invention provides liposomes prepared by a method that achieves a drug/lipid ratio of at least 0.06, two fold higher than that reported by Mori *et al.* Administration of these liposomes provides improved efficacy, due to the higher drug per lipid dose.

Since the combined teachings of Martin *et al.* and Mori *et al.* fail to show or suggest all of the claim limitations and fail to suggest to one of skill in the art that liposomes with a drug/lipid ratio of 0.06-0.67 could be achieved, the present claims are

not obvious in view of these documents. Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

D. Analysis: Rejection over Martin *et al.* in view of Mori *et al.* and further in view of Kassis *et al.*

The comments above apply to the rejection based on Martin *et al.* in view of Mori *et al.* and further in view of Kassis *et al.* Specifically, the documents taken together do not provide a liposome composition having a drug/lipid ratio of between 0.06-0.67. For the reasons given above, one of skill would not expect that liposomes including a lipid-derivatized radiosensitizer could be prepared to have greater than about 3 mol%, which correlates to a drug/lipid ratio of 0.03.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

VI. Conclusion

In view of the foregoing, the claims pending in the application comply with the requirements of 35 U.S.C. § 112 and patentably define over the applied art. A Notice of Allowance is, therefore, respectfully requested. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 564-2867.

Respectfully submitted,

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Judy M. Mohr
Registration No. 38,563

Correspondence Address:
Customer Number 27777
ALZA Corporation
1900 Charleston Road
P.O. Box 7210, M10-3
Mountain View, CA 94039-7210

APPENDIX A

Analysis of Liposomal Composition of Invention: 89/5/6

Component (molecular weight)	Mole Fraction	Mole Percent[1]	Weight of each component[2] (g)	Weight Percent[3]	Drug/Lipid (wt/wt)[4]	Drug/Lipid (mol/mol)
HSPC (762 g/mol)	89	89	678.2	78.1	0.06	0.06
mPEG-DSPE (2800 g/mol)	5	5	140	16.1		
dplUdR (830.9 g/mol)	6	6	49.8	5.7		

[1][(mole fraction of each component) / (sum of component mole fractions)] x 100
[2](mole fraction of each component) x (molecular weight of each component)
[3](weight of each component) / (sum of component weights)
[4](weight dplUdR) / (sum of lipid weights)
[5](mole fraction of dplUdR) / (sum of lipid mole fractions)

Analysis of Liposomal Composition of Invention: 80/5/15

Component (molecular weight)	Mole Fraction	Mole Percent[1]	Weight of each component[2] (g)	Weight Percent[3]	Drug/Lipid Ratio[4] (wt/wt)	Drug/Lipid Ratio[5] (mol/mol)
HSPC (762 g/mol)	80	80	609.6	69.7	0.17	0.18
mPEG-DSPE (2800 g/mol)	5	5	140	16.0		
dplUdR (830.9 g/mol)	15	15	124.6	14.2		

[1][(mole fraction of each component) / (sum of component mole fractions)] x 100
[2](mole fraction of each component) x (molecular weight of each component)
[3](weight of each component) / (sum of component weights)
[4](weight dplUdR) / (sum of lipid weights)
[5](mole fraction of dplUdR) / (sum of lipid mole fractions)

Analysis of Mori *et al.* Liposomal Composition

Component (molecular weight)	Mole Ratio[1]	Mole Percent[2]	Weight of each component[3] (g)	Weight Percent[4]	Drug/Lipid (wt/wt)[5]	Drug/Lipid (mol/mol)[6]
Egg PC (760 g/mol)	10	60	456.0	66.1	0.032	0.031
Cholesterol (386 g/mol)	5	30	115.8	16.8		
Monosialo-ganglioside (GM_1) (1564 g/mol)	1	6	93.8	13.6		
Octyl-glucopyranoside (OG) (292.4 g/mol)		1	2.9	0.4		
dpFUdR (723 g/mol)	-	3	21.7	3.1		

[1]Composition is described as having dpFUdR "at 3.0 mol% of the lipid mixture" (page 449, Col. 1, lines 1-3 of section entitled "Liposome Preparation") and OG at "1.0 mol% of the lipid mixture"; therefore the mixture is 96 mol% lipid and 3 mol% drug. The 96% lipid fraction is comprised of PC/Chol/GM_1 at molar ratios of 10/5/1.
[2] calculated as follows: [(component mole ratio/sum of mole ratios) x 96% lipid phase]; egg PC: (10/16) x 96%; Cholesterol: [(5/16) x 96%; mPEG-DSPE: (1/16) x 96%; dpFUdR is given as 3 mole percent.
[3](mole percent of each component) x (molecular weight of each component)
[4](weight of each component) / (sum of component weights)
[5](3.1/(66.1 + 16.8 + 13.6))
[6](mole percent of dpFUdR) / (sum of lipid mole percentages)